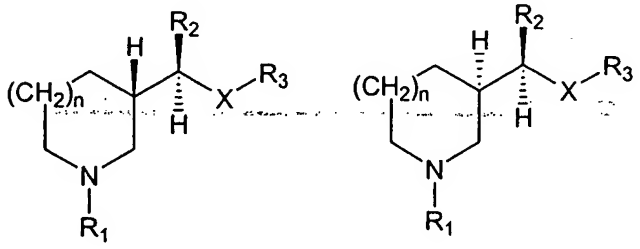
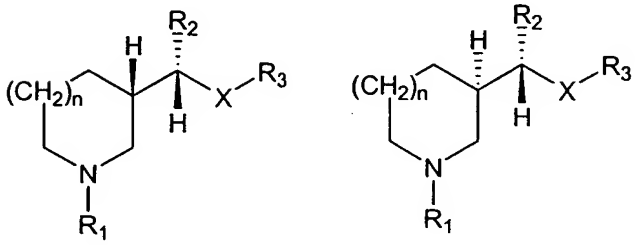
Figure 1

Examples of Substituted Piperidines Accessible Via the Methods of the Present Invention



Structure A **Structure B**



Structure C **Structure D**

For Structures A, B, C, and D:

n = 0, 1, or 2
R_1 = H, alkyl, aryl, heteroaryl, aralkyl, $-CO_2R_4$, or $-C(O)NHR_4$
R_2 = alkyl
X = O, $NC(O)R_4$, or $NS(O)_2R_4$, NH, NR_4, S, or S(O)
R_3 = alkyl, aralkyl, aryl, or heteroaryl
R_4 = alkyl, aryl, heteroaryl, or aralkyl

Figure 2

Prophetic Asymmetric Synthesis of 3-Substituted Piperidine 1

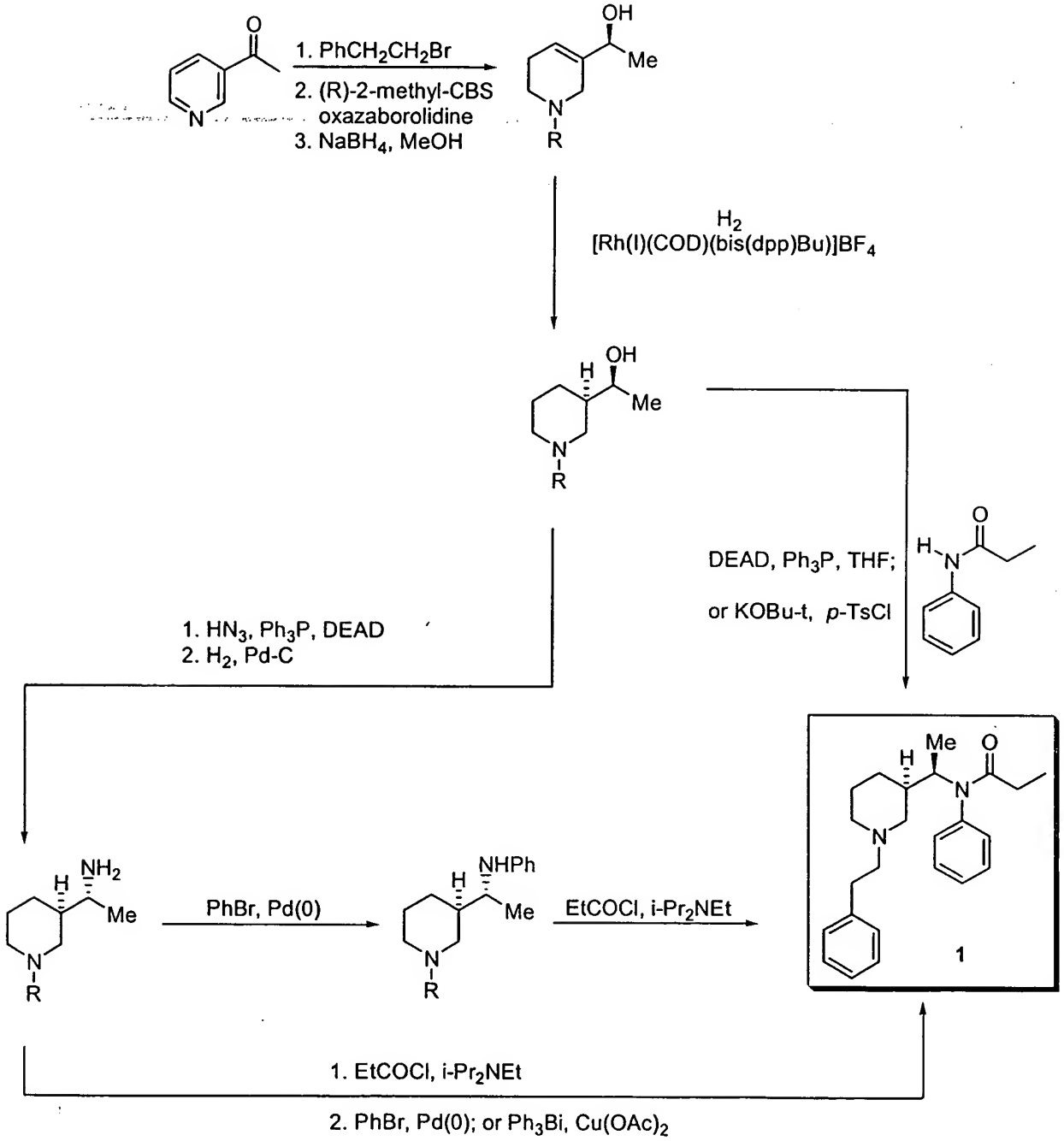


Figure 3

Prophetic Asymmetric Synthesis of 50

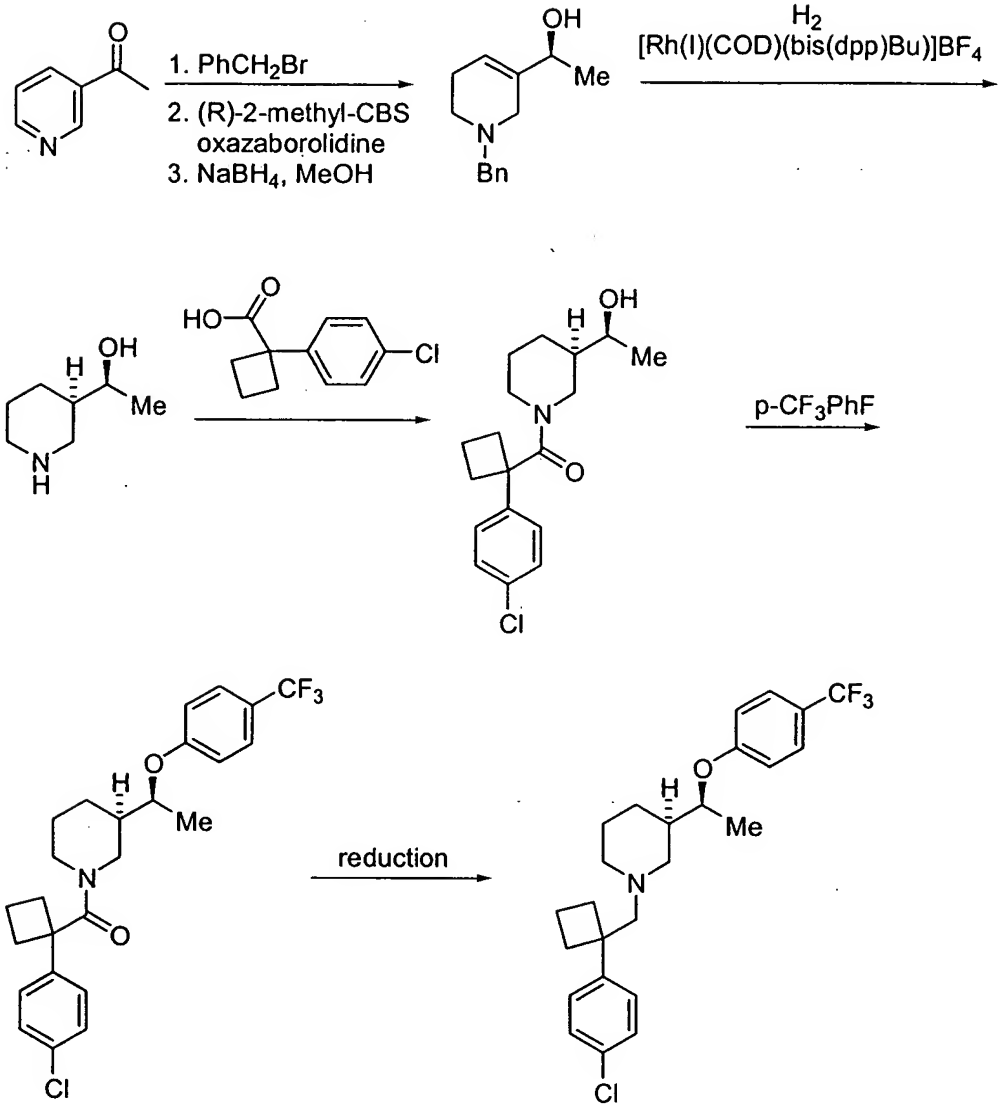


Figure 4

Prophetic Asymmetric Syntheses of 3-Substituted Piperidine 1

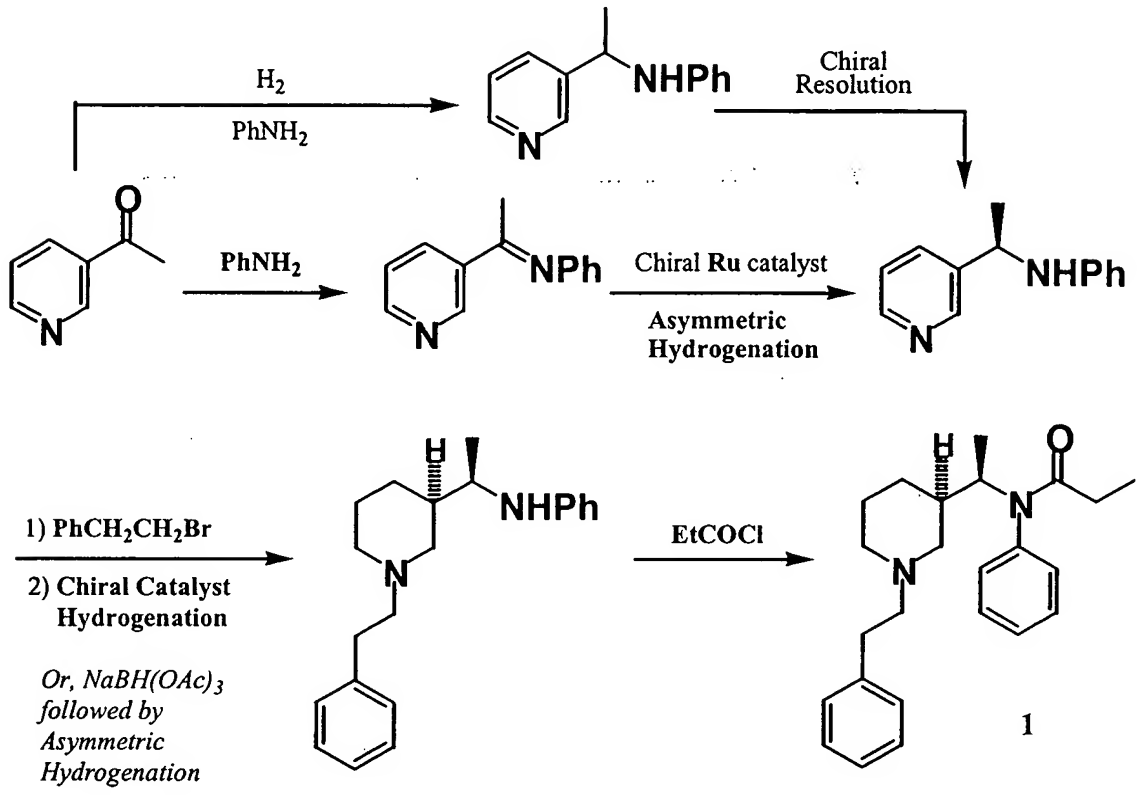
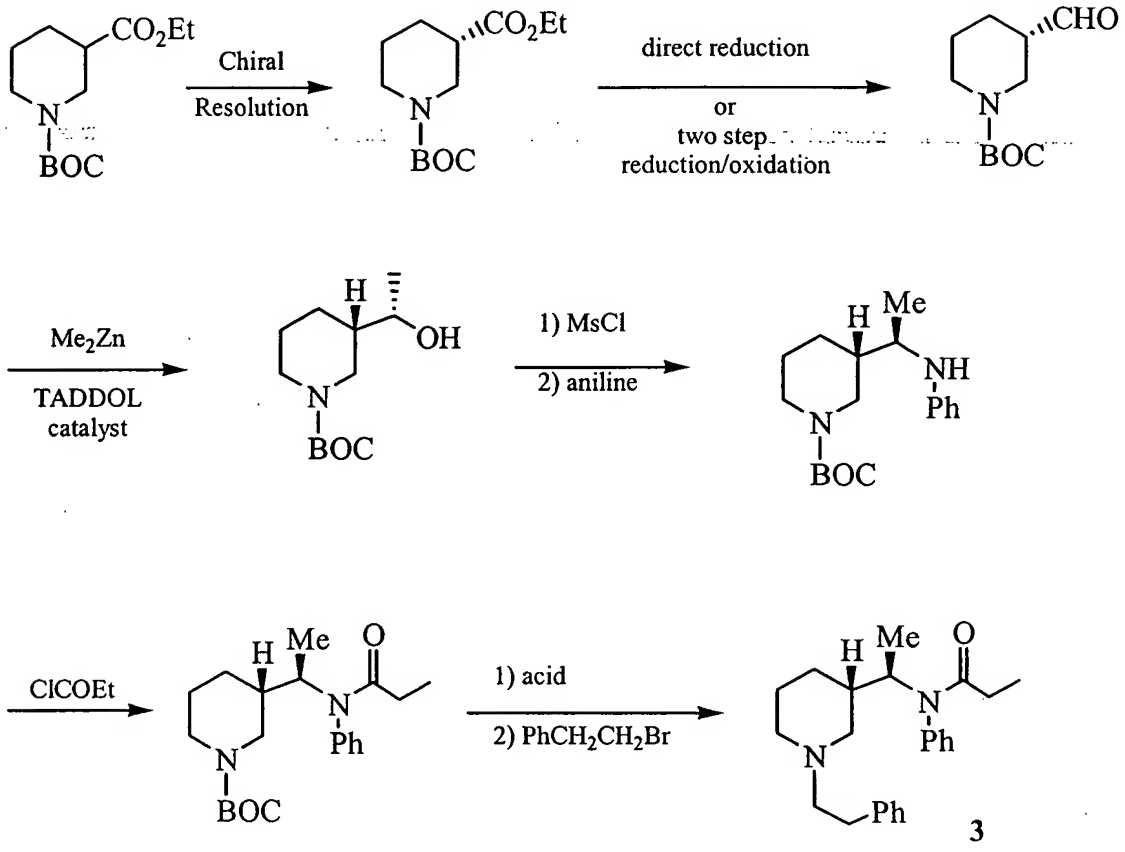


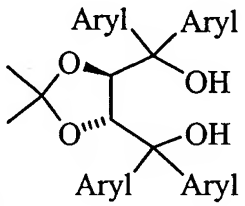
Figure 5

Prophetic Asymmetric Synthesis of 3-Substituted Piperidine 3



TADDOL catalysts

Aryl = Ph,
2-napthyl, or 1-napthyl



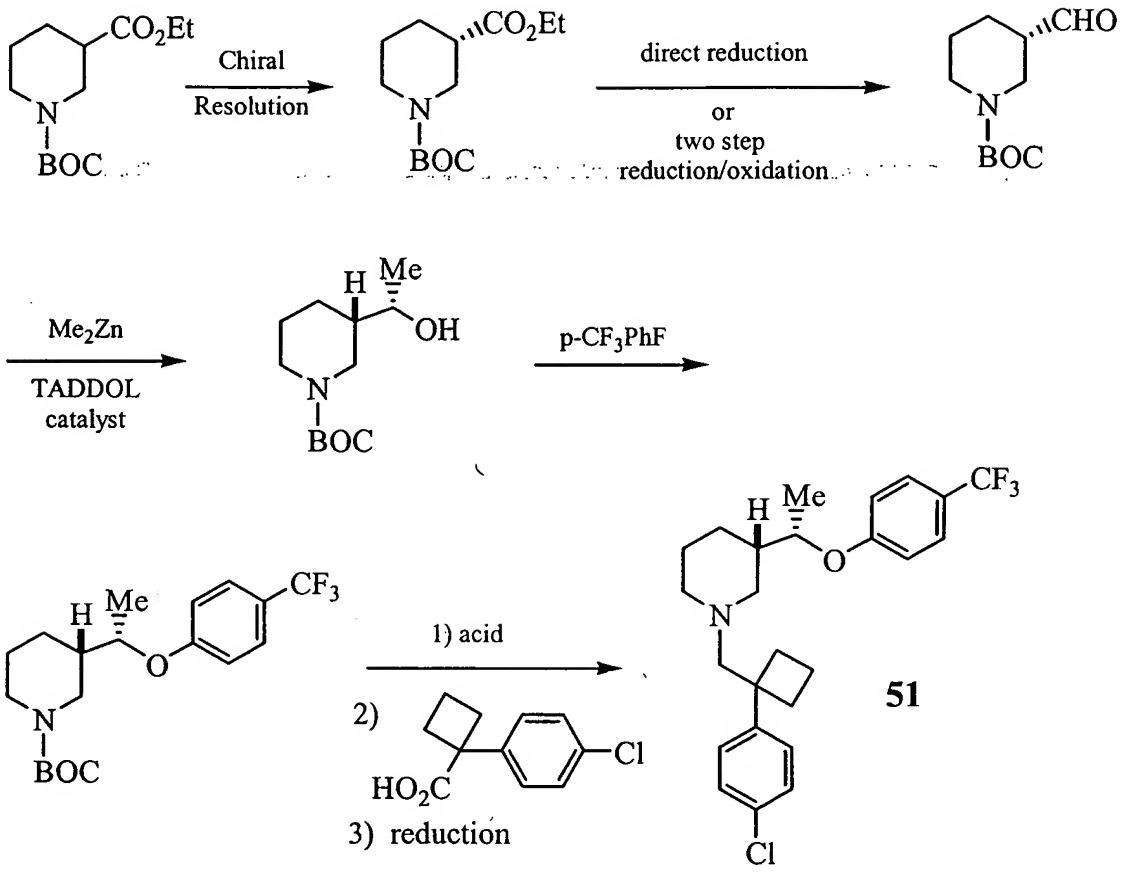
+ $Ti(O\text{-}i\text{-}Pr)_4$

Both enantiomers are commercially available

See Seebach, D. et al.
Tetrahedron **1992,** *48* (27), 5719.

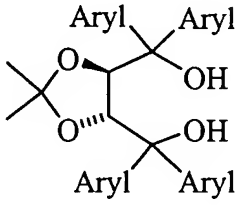
Figure 6

Prophetic Asymmetric Synthesis of 3-Substituted Piperidine 51



TADDOL catalysts

Aryl = Ph,
2-napthyl, or 1-napthyl



+ $Ti(O\text{-}i\text{-}Pr)_4$

Both enantiomers are commercially available

See Seebach, D. et al.
Tetrahedron **1992,** *48* (27), 5719.

Figure 7

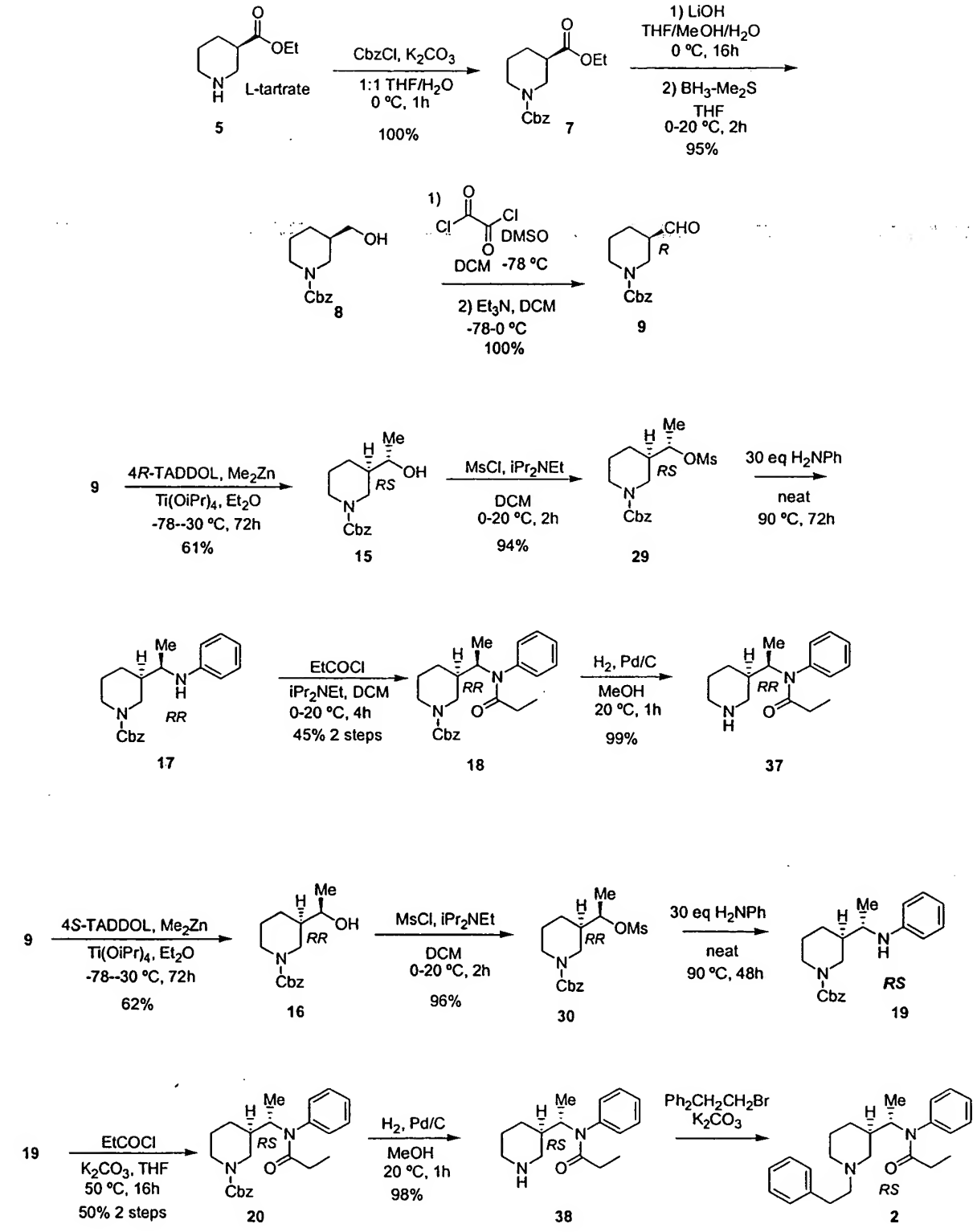

L-tartrate
5
CbzCl, K2CO3
1:1 THF/H2O
0 °C, 1h
100%
7
1) LiOH
THF/MeOH/H2O
0 °C, 16h
2) BH3-Me2S
THF
0-20 °C, 2h
95%
8
1)
DMSO
DCM -78 °C
2) Et3N, DCM
-78-0 °C
100%
9
4R-TADDOL, Me2Zn
Ti(OiPr)4, Et2O
-78--30 °C, 72h
61%
15
MsCl, iPr2NEt
DCM
0-20 °C, 2h
94%
29
30 eq H2NPh
neat
90 °C, 72h
17
EtCOCl
iPr2NEt, DCM
0-20 °C, 4h
45% 2 steps
18
H2, Pd/C
MeOH
20 °C, 1h
99%
37
4S-TADDOL, Me2Zn
Ti(OiPr)4, Et2O
-78--30 °C, 72h
62%
16
MsCl, iPr2NEt
DCM
0-20 °C, 2h
96%
30
30 eq H2NPh
neat
90 °C, 48h
19
EtCOCl
K2CO3, THF
50 °C, 16h
50% 2 steps
20
H2, Pd/C
MeOH
20 °C, 1h
98%
38
Ph2CH2CH2Br
K2CO3
2

Figure 8

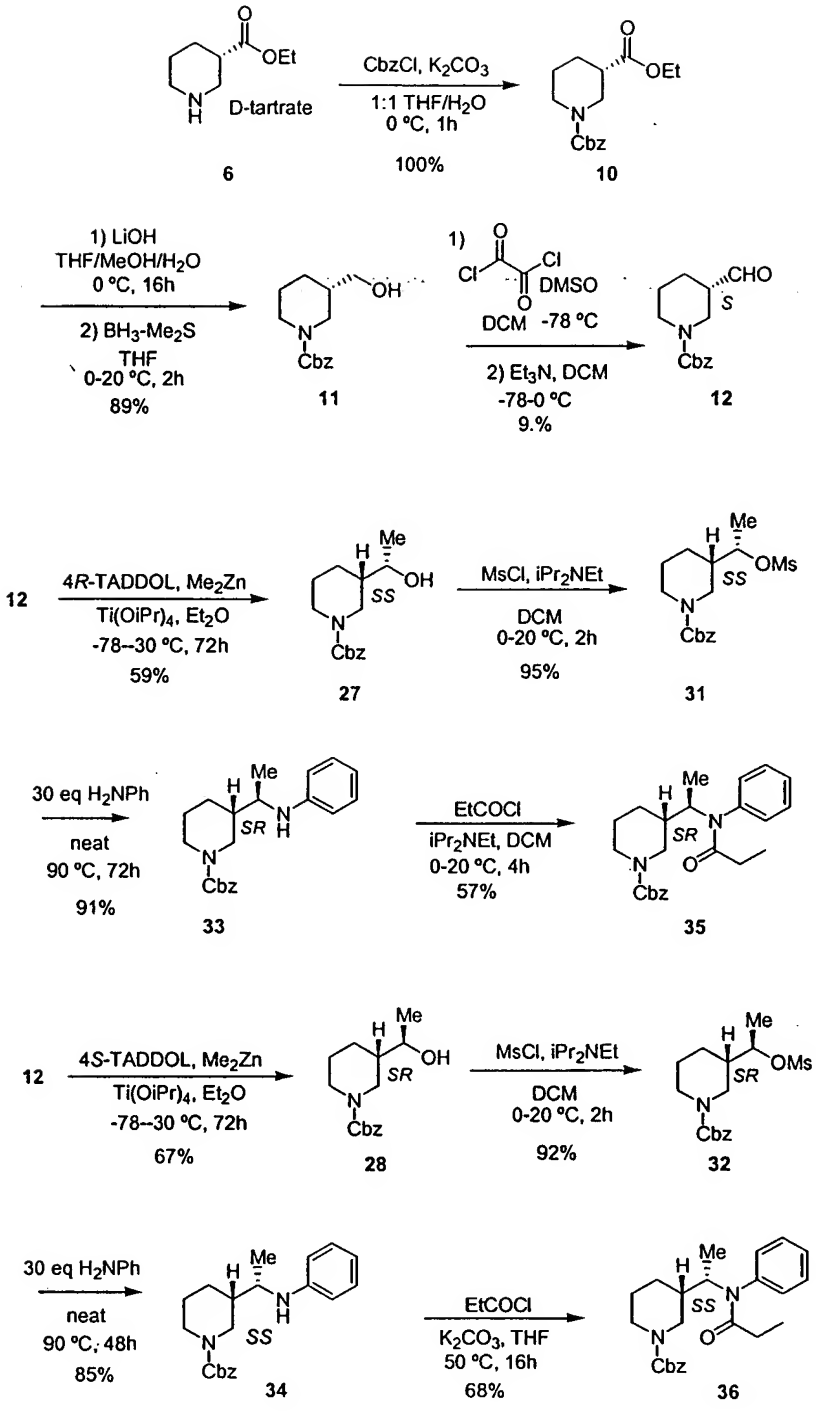

D-tartrate
6
CbzCl, K2CO3
1:1 THF/H2O
0 °C, 1h
100%
10
1) LiOH
THF/MeOH/H2O
0 °C, 16h
2) BH3-Me2S
THF
0-20 °C, 2h
89%
11
1)
DMSO
DCM -78 °C
2) Et3N, DCM
-78-0 °C
9.%
12
12
4R-TADDOL, Me2Zn
Ti(OiPr)4, Et2O
-78--30 °C, 72h
59%
27
MsCl, iPr2NEt
DCM
0-20 °C, 2h
95%
31
30 eq H2NPh
neat
90 °C, 72h
91%
33
EtCOCl
iPr2NEt, DCM
0-20 °C, 4h
57%
35
12
4S-TADDOL, Me2Zn
Ti(OiPr)4, Et2O
-78--30 °C, 72h
67%
28
MsCl, iPr2NEt
DCM
0-20 °C, 2h
92%
32
30 eq H2NPh
neat
90 °C, 48h
85%
34
EtCOCl
K2CO3, THF
50 °C, 16h
68%
36

Figure 9

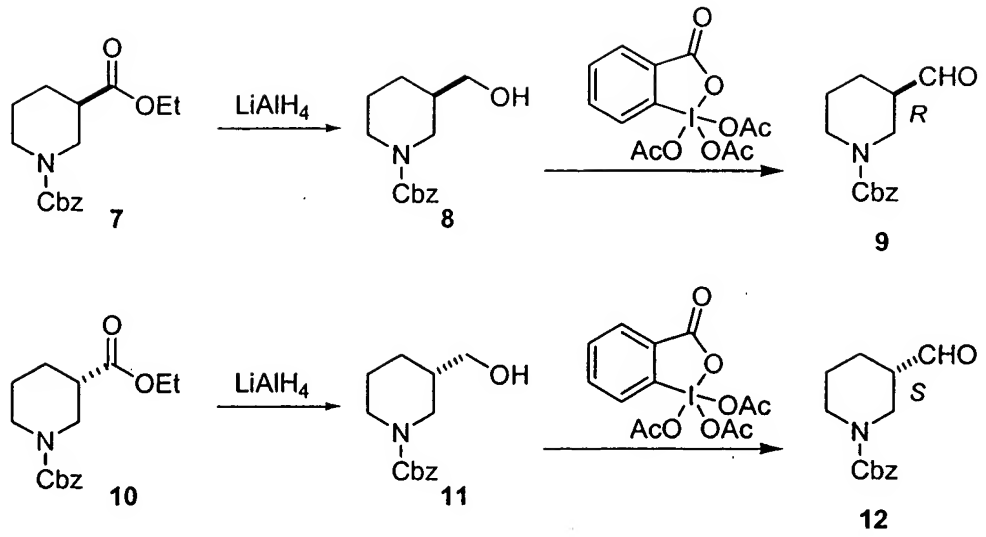


Figure 10

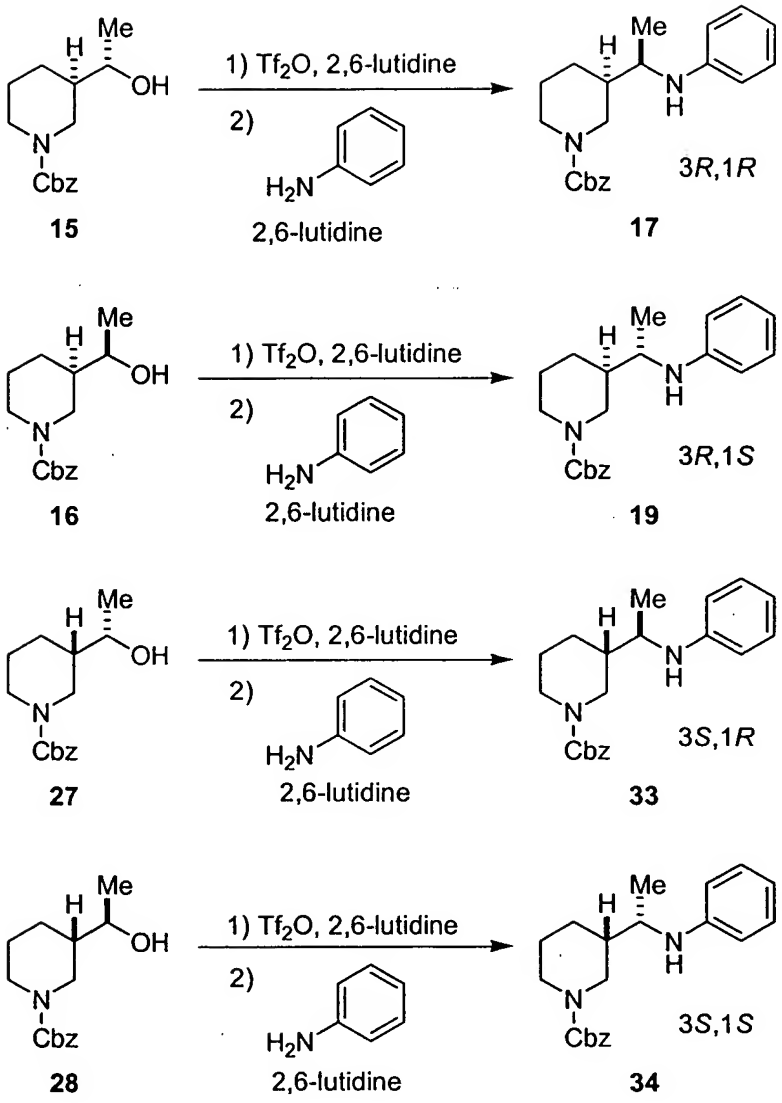

Me
H
OH
N
Cbz
15
1) Tf2O, 2,6-lutidine
2)
H2N
2,6-lutidine
Me
H
N
H
N
Cbz
3R,1R
17
Me
H
OH
N
Cbz
16
1) Tf2O, 2,6-lutidine
2)
H2N
2,6-lutidine
Me
H
N
H
N
Cbz
3R,1S
19
Me
H
OH
N
Cbz
27
1) Tf2O, 2,6-lutidine
2)
H2N
2,6-lutidine
Me
H
N
H
N
Cbz
3S,1R
33
Me
H
OH
N
Cbz
28
1) Tf2O, 2,6-lutidine
2)
H2N
2,6-lutidine
Me
H
N
H
N
Cbz
3S,1S
34

Figure 11

Mixture of 15, 16, 27, and 28

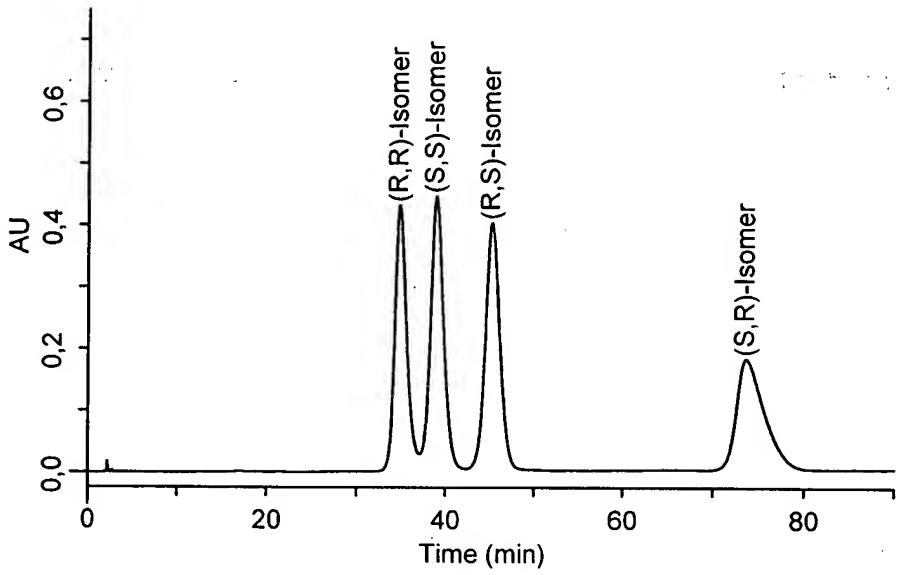


Figure 12

15: (R,S)-Isomer Chromatogram

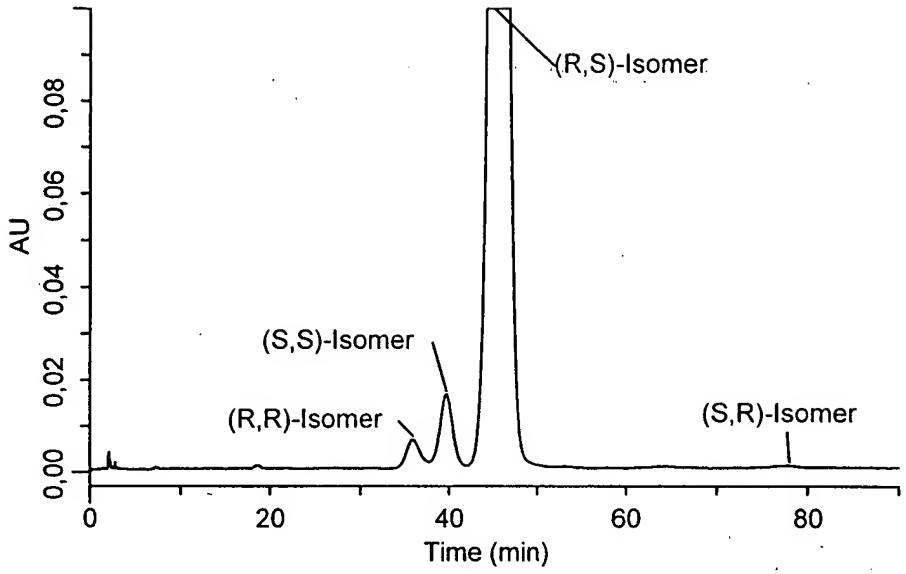


Figure 13

27: (S,S)-Isomer Chromatogram

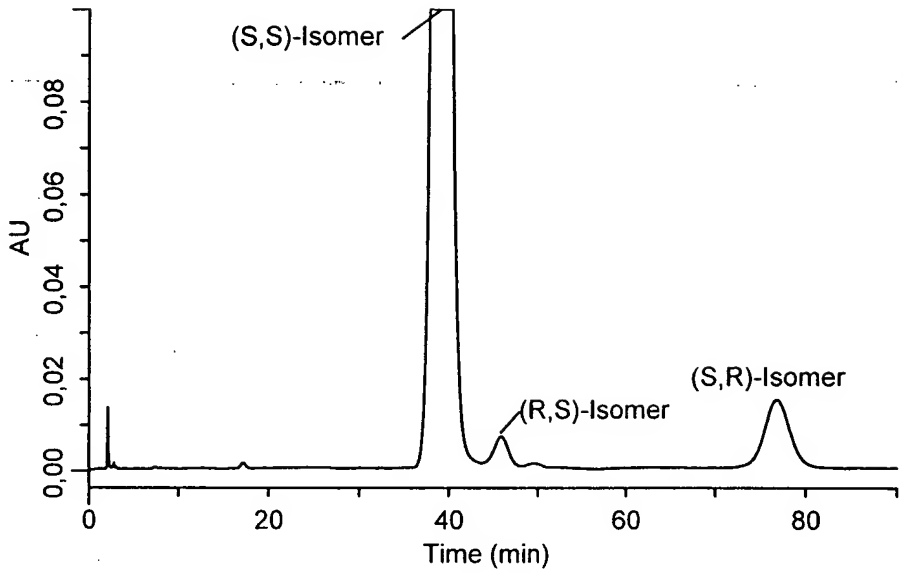


Figure 14

16: (R,R)-Isomer Chromatogram

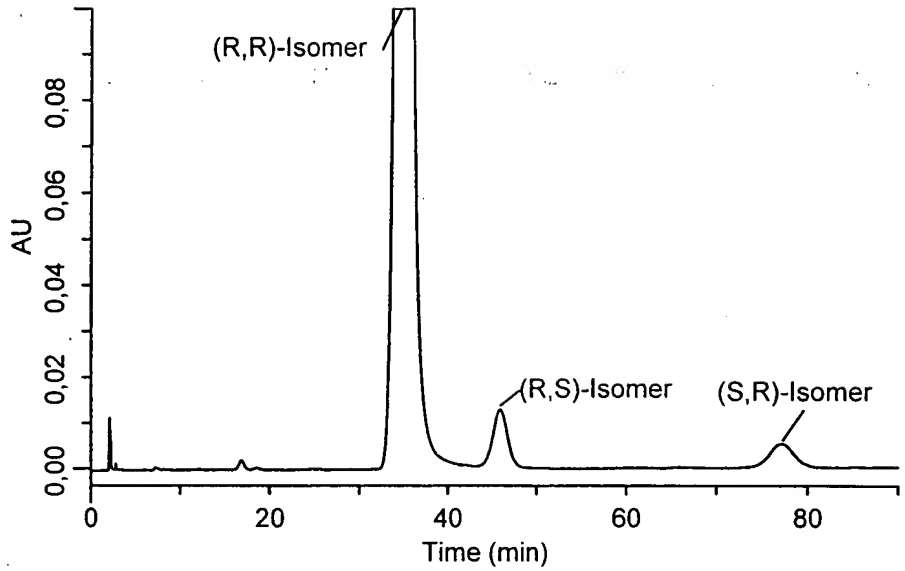


Figure 15

28: (S,R)-Isomer Chromatogram

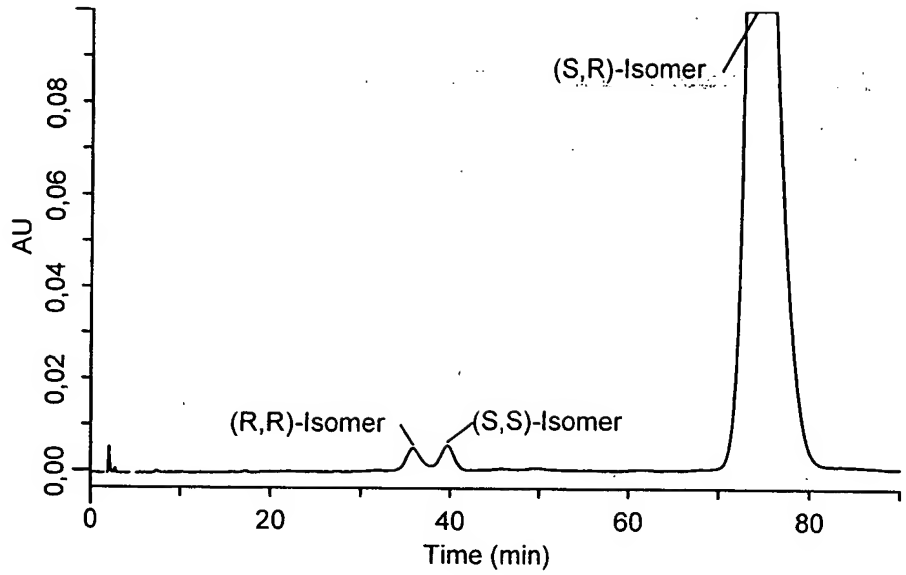


Figure 16

No.	Description of HPLC Trace	Peak Retention Times (min)
1	Catalyst 13 (254 nm)	8.420, 8.781
2	Catalyst 13 (220 nm)	8.420, 8.781
3	Catalyst 13 and non-selective coinjection (254 nm)	8.155, 8.328, 8.695
4	Catalyst 13 and non-selective coinjection (220 nm)	8.155, 8.333, 8.688
5	non-selective (254 nm)	8.208, 8.395, 8.688
6	Catalyst 14 (254 nm)	8.061, 8.210, 8.399, 8.688, 8.897

Figure 17

No.	Description of HPLC Trace	Peak Retention Times (min)
1	Catalyst 14 (254 nm)	8.158, 8.423
2	Catalyst 14 (220 nm)	8.030, 8.159, 8.366
3	Catalyst 14 and non-selective coinjection (254 nm)	8.176, 8.386, 8.664
4	Catalyst 14 and non-selective coinjection (220 nm)	8.044, 8.178, 8.387
5	non-selective (254 nm)	8.176, 8.374, 8.646, 9.950
6	non-selective (220 nm)	8.375

Figure 18

No.	Description of HPLC Trace	Peak Retention Times (min)
1	Catalyst 13 (254 nm)	8.42
2	Catalyst 13 (220 nm)	8.420, 8.781
3	Catalyst 13 and Catalyst 14 coinjection (254 nm)	8.147, 8.337, 8.695
4	Catalyst 13 and Catalyst 14 coinjection (220 nm)	8.147, 8.338, 8.695
5	Catalyst 14 (254 nm)	8.158, 8.423
6	Catalyst 14 (220 nm)	8.030, 8.159, 8.366

Figure 19

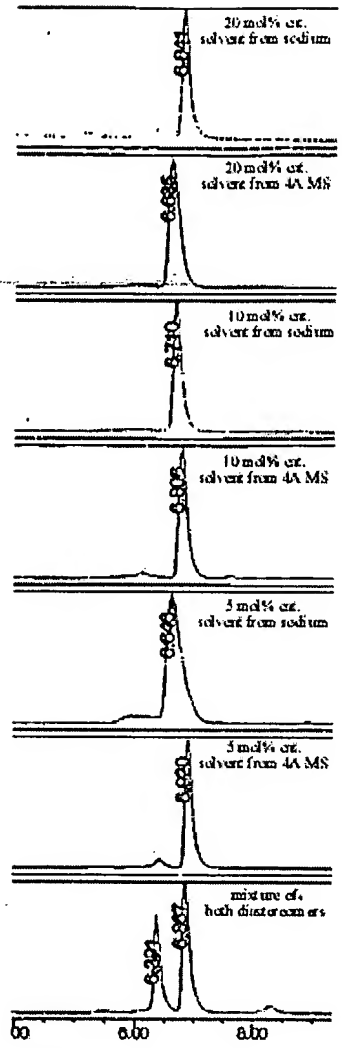

20 mol% cat.
solvent from sodium
20 mol% cat.
solvent from 4A MS
10 mol% cat.
solvent from sodium
10 mol% cat.
solvent from 4A MS
5 mol% cat.
solvent from sodium
5 mol% cat.
solvent from 4A MS
mixture of
both diastereomers
6.00
8.00

Figure 20

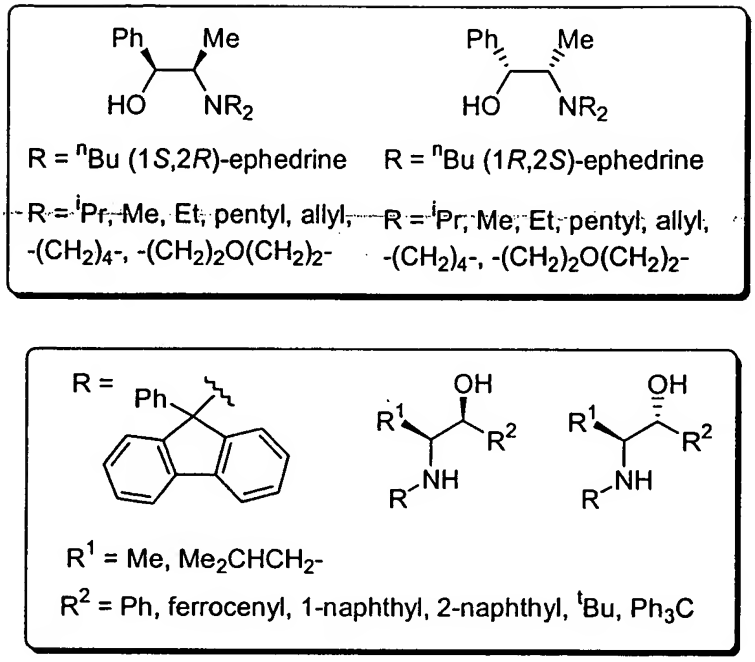
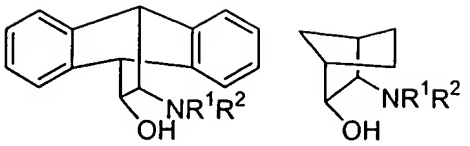
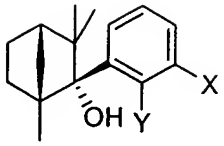

Ph
Me
HO
NR2
R = nBu (1S,2R)-ephedrine
R = iPr, Me, Et, pentyl, allyl, -(CH2)4-, -(CH2)2O(CH2)2-
Ph
Me
HO
NR2
R = nBu (1R,2S)-ephedrine
R = iPr, Me, Et, pentyl, allyl, -(CH2)4-, -(CH2)2O(CH2)2-
R =
Ph
OH
R1
R2
NH
R
OH
R1
R2
NH
R
R1 = Me, Me2CHCH2-
R2 = Ph, ferrocenyl, 1-naphthyl, 2-naphthyl, tBu, Ph3C
R2N
HO
R1
R1
R = nBu, Me, H
R1 = nBu, Ph
NMe2
OH
(-)-DAIB
BnO
nBu2N
HO
nBu
nBu
NHBu
BuO
OH
R
R
R = Ph, nBu
NBu2
OH
Bz
N
Me
HO

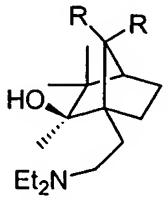
Figure 21



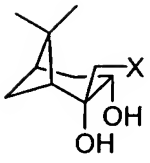
$R^1 = R^2 = Me$
$R^1 = SO_3CF_3$, $R^2 = H$

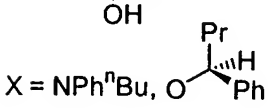


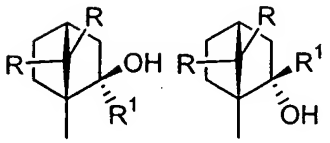
X = H, $SiMe_3$
Y = $-CH_2NMe_2$, OMe



R = H, Me







R = H, Me

R^1 = $-(CH_2)_3NMe_2$, 2-(Me_2N)Ph, 2-pyridyl, 2-*N*-Me-pyrrolyl, $-(CH(OH))CH_2NMe_2$

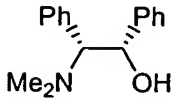
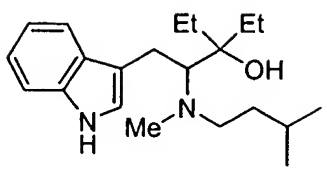
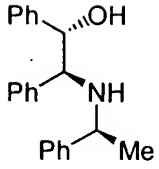
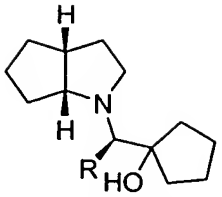


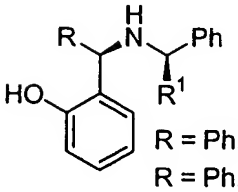
Figure 22



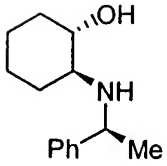


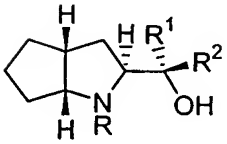


R = Me, Ph

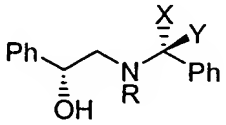


R = Ph, R^1 = Me, H
R = Ph, H, R^1 = Me

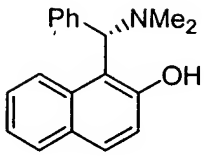


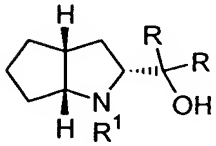


R = H, Me
R^1 = H, R^2 = p-tolyl
R^1 = p-tolyl, R^2 = H



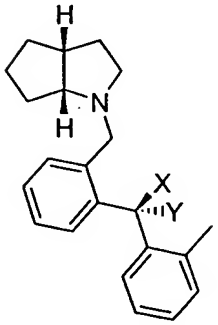
R = H, Me
X = H, Y = Me
X = Me, Y = H





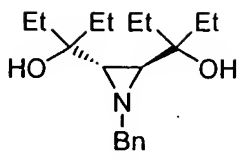
R = Ph, Et, Pr, ^{n}Bu,
-$(CH_2)_4$-, CH_2Ph

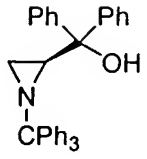
R^1 = H, Me

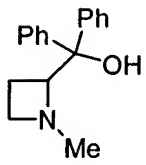


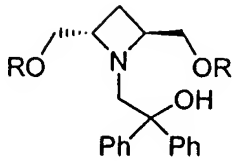
X = H, Y = OH
X = OH, Y = H

Figure 23

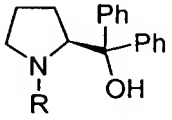


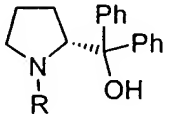




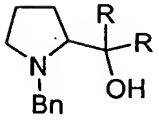


R = Me, TBDMS, TBDPS

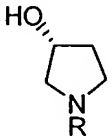




R = Me, H, -CH_2CMe_3

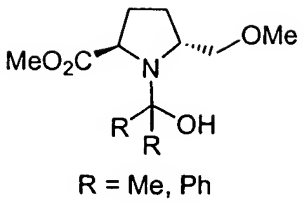


R = Me, Et, Ph

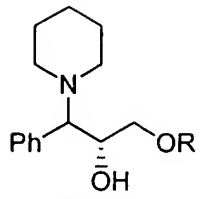


R = H, -(CH_2)-2-pyridyl,
-$(CH_2)C(Ph)_2OH$

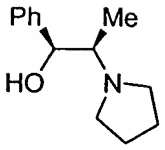
Figure 24

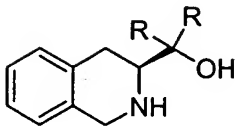


R = Me, Ph

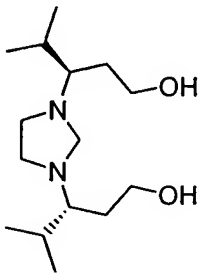


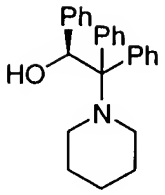
R = Me, TBDMS, TBDPS, Bn, CPh_3

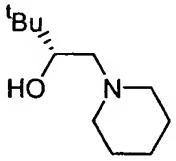


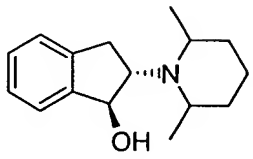


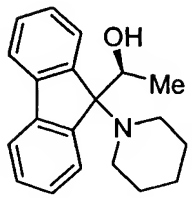
R = H, Ph











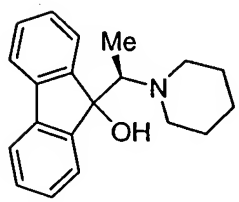
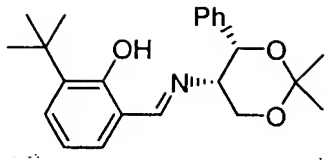
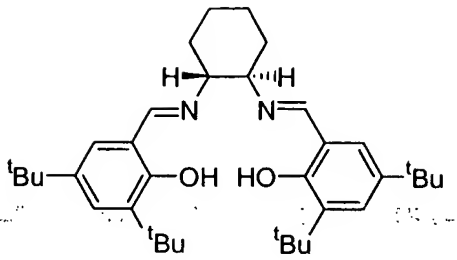
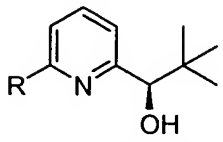


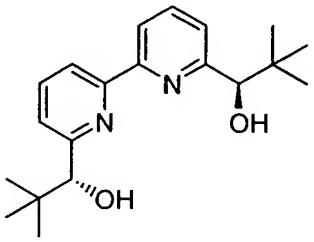
Figure 25

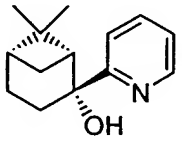


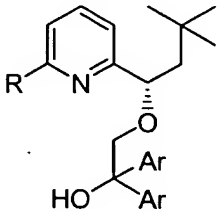




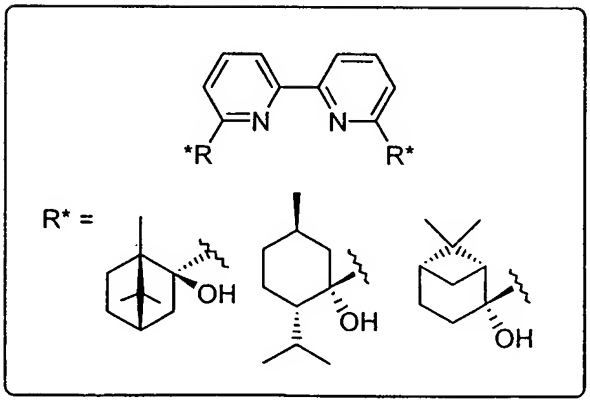
R = Br, Ph, 2-pyridyl, alkynyl, 2-naphthyl, 2-(MeO)Ph, H







Ar = Ph, 1-naphthyl, 2-naphthyl



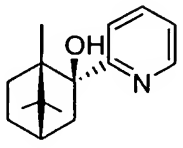
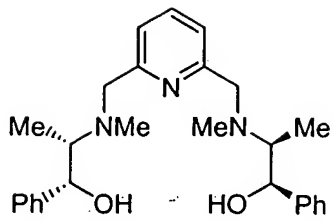
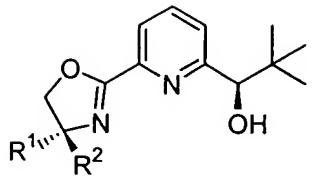
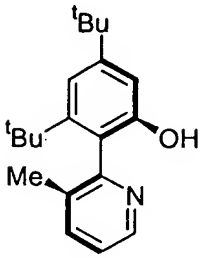


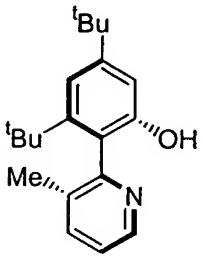
Figure 26

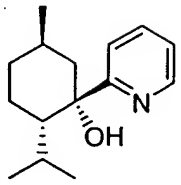


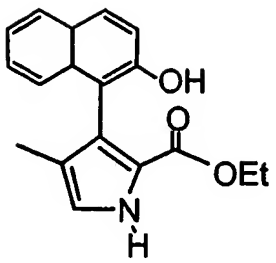


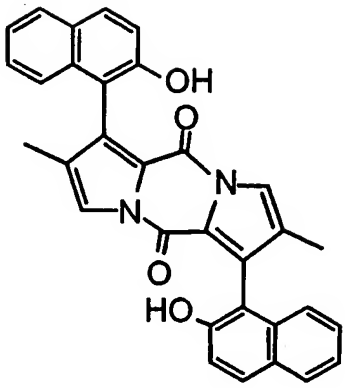
$R^1 = {}^iPr$, $R^2 = H$
$R^1 = H$, $R^2 = {}^iPr$

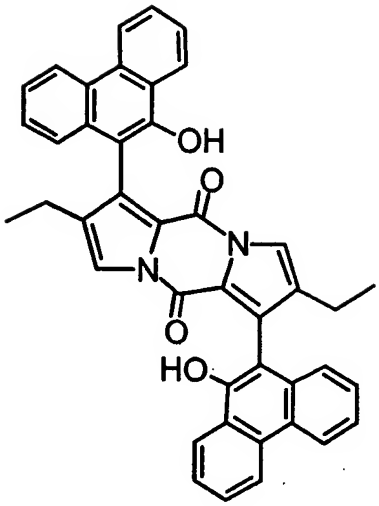


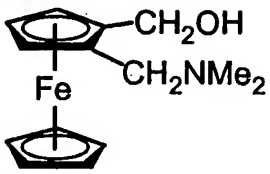


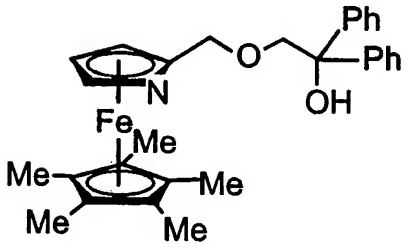


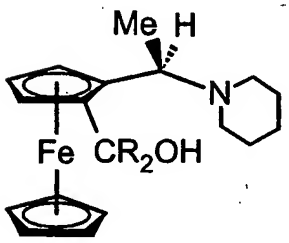




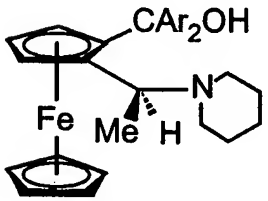




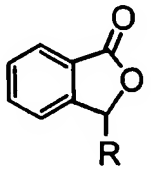




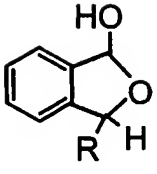
$R^1 = R^2 = Ph$
$R^1 = {}^1Bu, R^2 = Ph$
$R^1 = C_6F_5, R^2 = Ph$



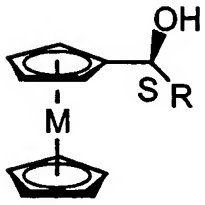
Ar = Ph
Ar = p-MeOPh
Ar = p-ClPh



R = Et, Bu

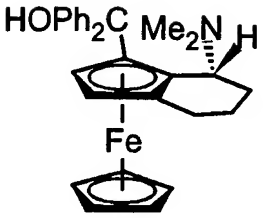


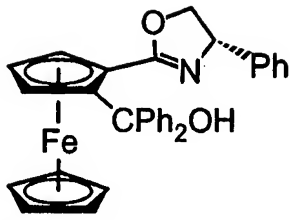
R = Et, ^{n}Bu

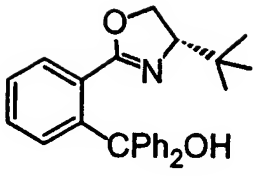


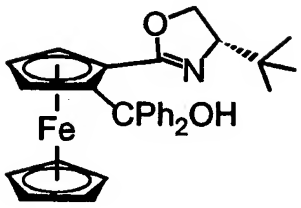
R = Me, Et

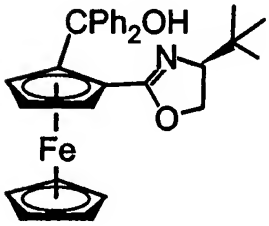
Figure 27

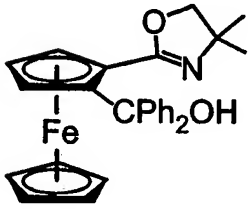


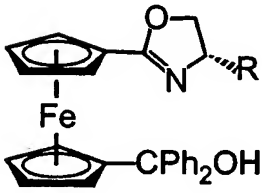




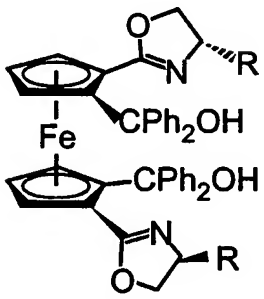




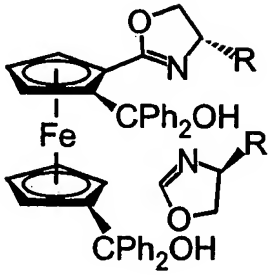




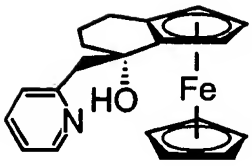
R = ^{1}Pr
R = Bn
R = ^{1}Bu
R = Ph

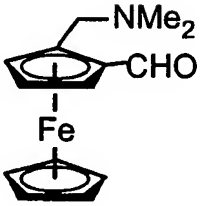


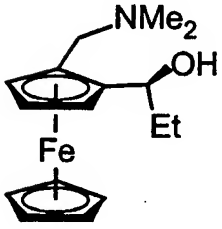
R = ^{1}Pr
R = ^{1}Bu

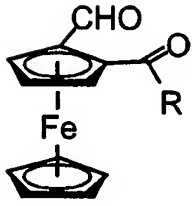


R = ^{1}Pr
R = ^{1}Bu







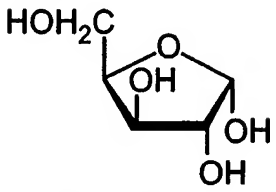


R = Ph
R = Bu
R = Me

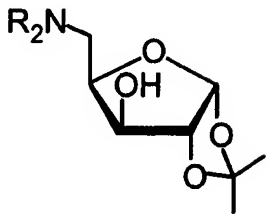
Figure 28

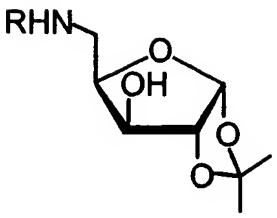
Figure 29

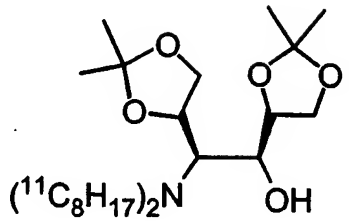
Aminoalcohols

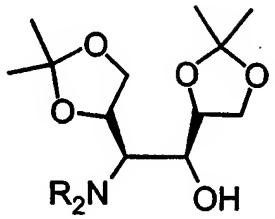


α-D-xylose

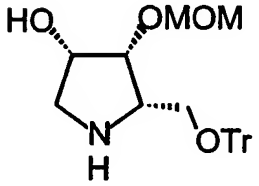


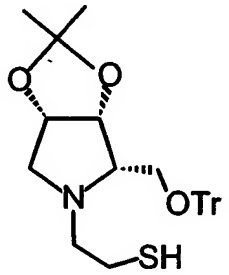


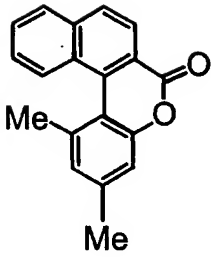


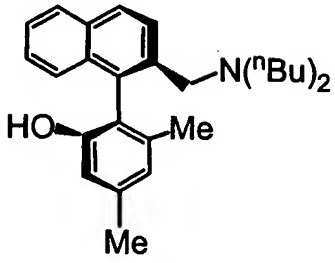


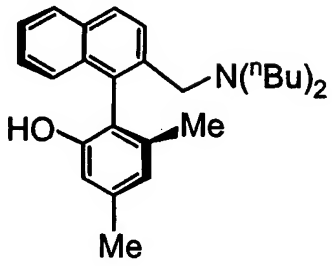
R = ^{n}Bu, -$(CH_2)_4$-,
-$(CH_2)_5$-, -$(CH_2)_6$-

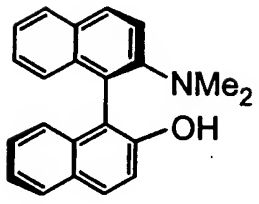


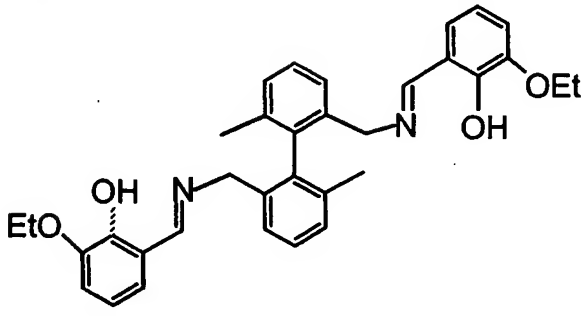


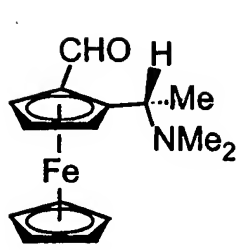


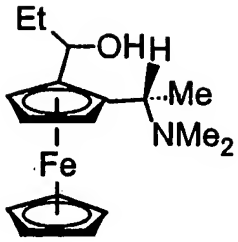


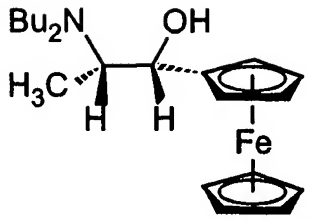


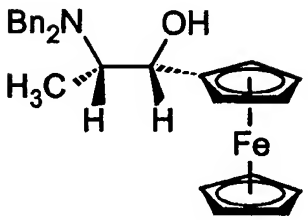


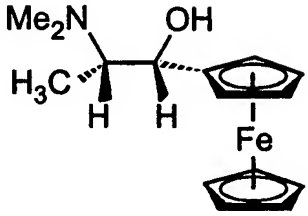


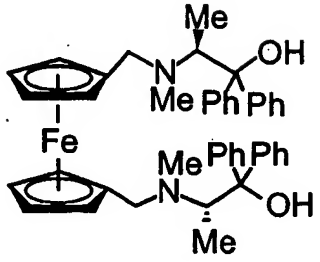


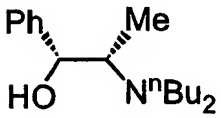


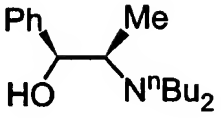


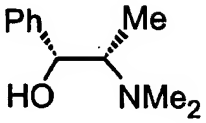


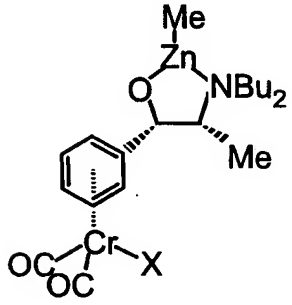




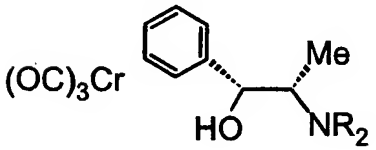




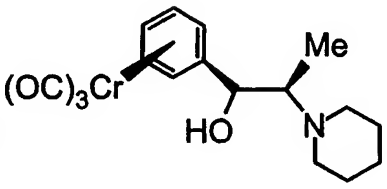


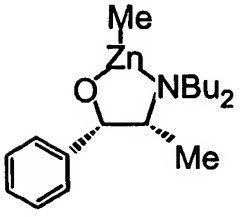


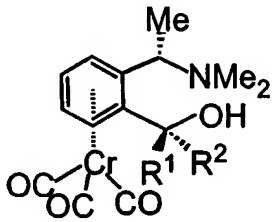
X = CO
X = $P(OEt)_3$
X = $P(OBu)_3$
X = $P(OPh)_3$



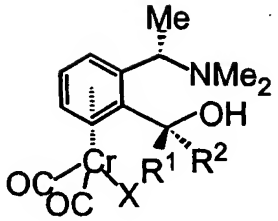
R = Me
R = ^{n}Bu







$R^1 = R^2 = Et$
$R^1 = R^2 = Ph$
$R^1 = Et, R^2 = H$



$R^1 = R^2 = Et, X = PPh_3$
$R^1 = R^2 = Ph, X = PPh_3$
$R^1 = R^2 = Et, X = P(OPh)_3$
$R^1 = Et, R^2 = H, X = PPh_3$
$R^1 = Et, R^2 = H, X = P(OPh)_3$

Figure 30

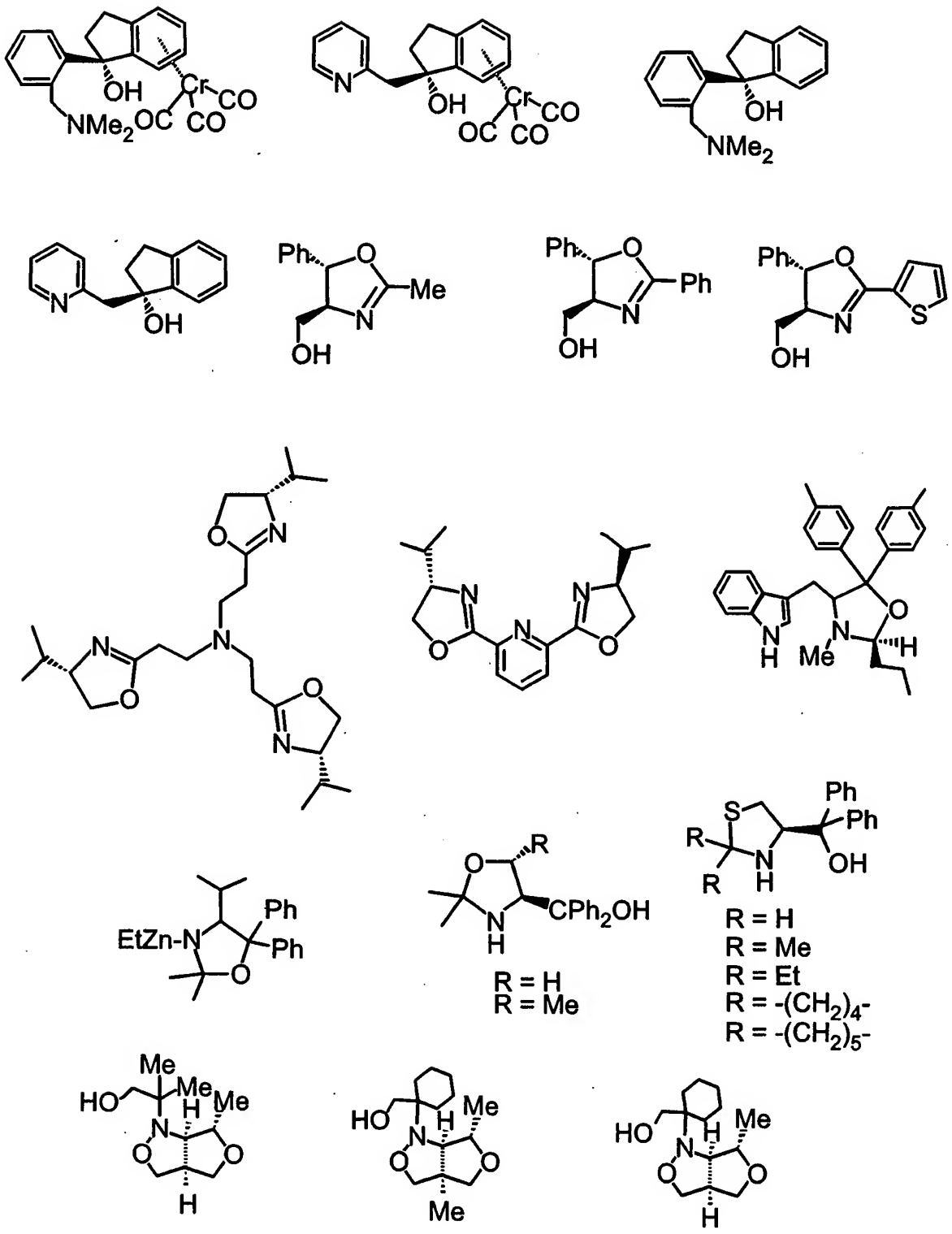
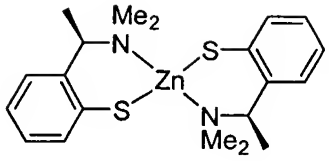
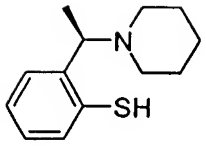
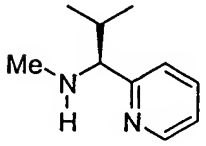

OH
Cr
CO
CO
CO
NMe2
N
OH
Cr
CO
CO
CO
OH
NMe2
N
OH
Ph
O
Me
N
OH
Ph
O
Ph
N
OH
Ph
O
S
N
OH
O
N
N
O
N
N
O
N
N
O
O
N
N
H
Me
N
O
H
EtZn-N
Ph
Ph
O
R
O
CPh2OH
N
H
R = H
R = Me
Ph
Ph
S
R
R
N
H
OH
R = H
R = Me
R = Et
R = -(CH2)4-
R = -(CH2)5-
Me
HO
Me
Me
H
N
O
O
H
HO
H
Me
N
O
O
Me
HO
H
Me
N
O
O
H

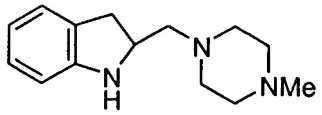
Figure 31

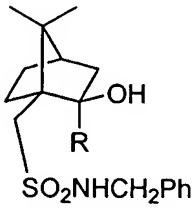
Figure 32



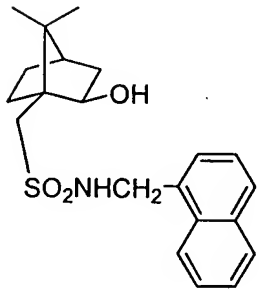


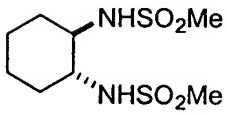






R = H, Me





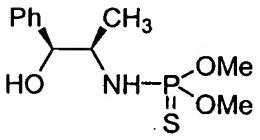
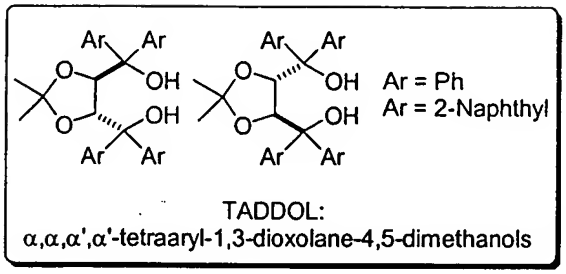
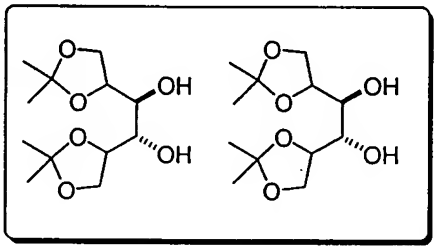
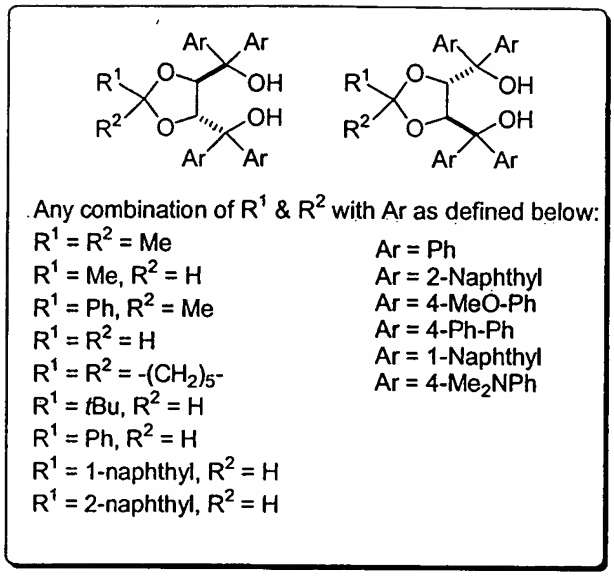
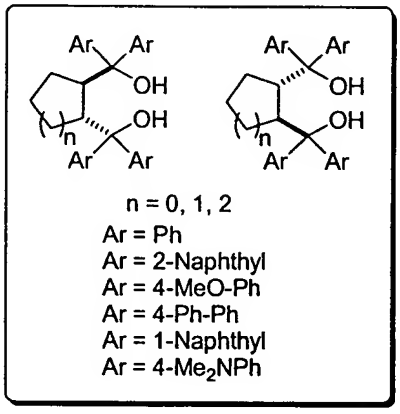


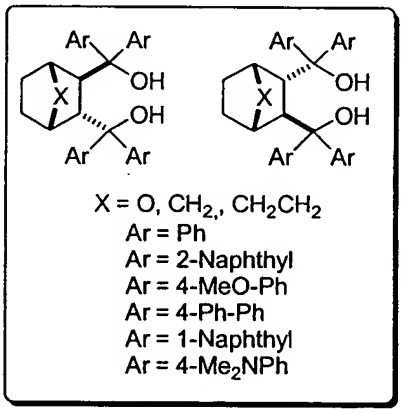
Figure 33

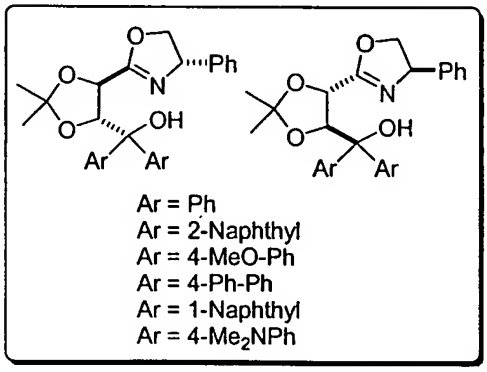

Ar = Ph
Ar = 2-Naphthyl
TADDOL:
α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols




Any combination of R1 & R2 with Ar as defined below:
R1 = R2 = Me
R1 = Me, R2 = H
R1 = Ph, R2 = Me
R1 = R2 = H
R1 = R2 = -(CH2)5-
R1 = tBu, R2 = H
R1 = Ph, R2 = H
R1 = 1-naphthyl, R2 = H
R1 = 2-naphthyl, R2 = H
Ar = Ph
Ar = 2-Naphthyl
Ar = 4-MeO-Ph
Ar = 4-Ph-Ph
Ar = 1-Naphthyl
Ar = 4-Me2NPh


n = 0, 1, 2
Ar = Ph
Ar = 2-Naphthyl
Ar = 4-MeO-Ph
Ar = 4-Ph-Ph
Ar = 1-Naphthyl
Ar = 4-Me2NPh


X = O, CH2,, CH2CH2
Ar = Ph
Ar = 2-Naphthyl
Ar = 4-MeO-Ph
Ar = 4-Ph-Ph
Ar = 1-Naphthyl
Ar = 4-Me2NPh


Ar = Ph
Ar = 2-Naphthyl
Ar = 4-MeO-Ph
Ar = 4-Ph-Ph
Ar = 1-Naphthyl
Ar = 4-Me2NPh

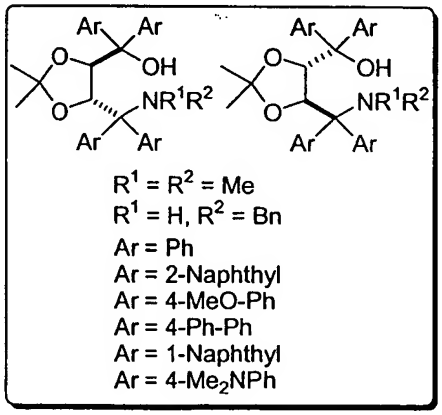

R1 = R2 = Me
R1 = H, R2 = Bn
Ar = Ph
Ar = 2-Naphthyl
Ar = 4-MeO-Ph
Ar = 4-Ph-Ph
Ar = 1-Naphthyl
Ar = 4-Me2NPh

Figure 34

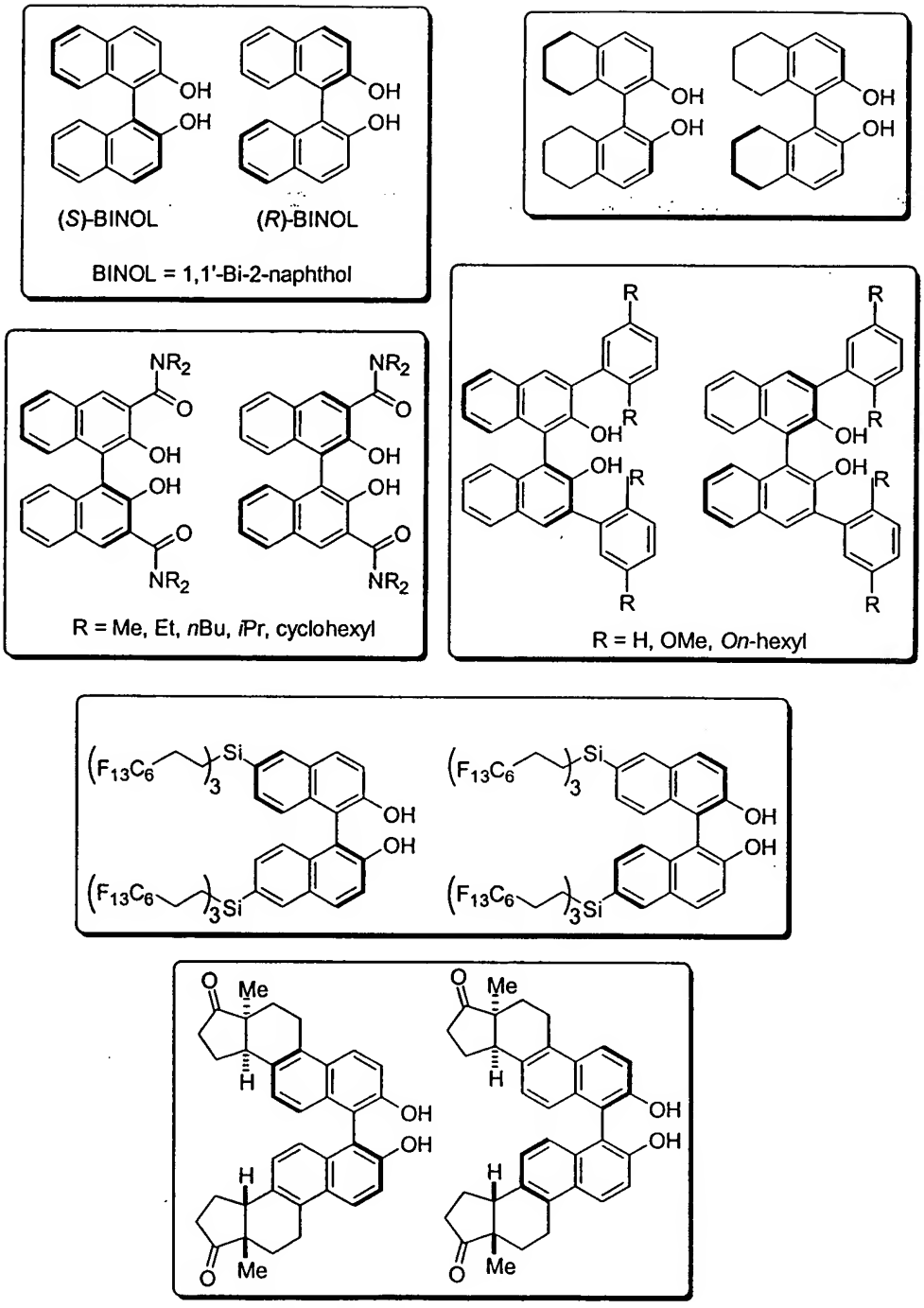

(S)-BINOL
(R)-BINOL
BINOL = 1,1'-Bi-2-naphthol
R = Me, Et, nBu, iPr, cyclohexyl
R = H, OMe, On-hexyl

Figure 35

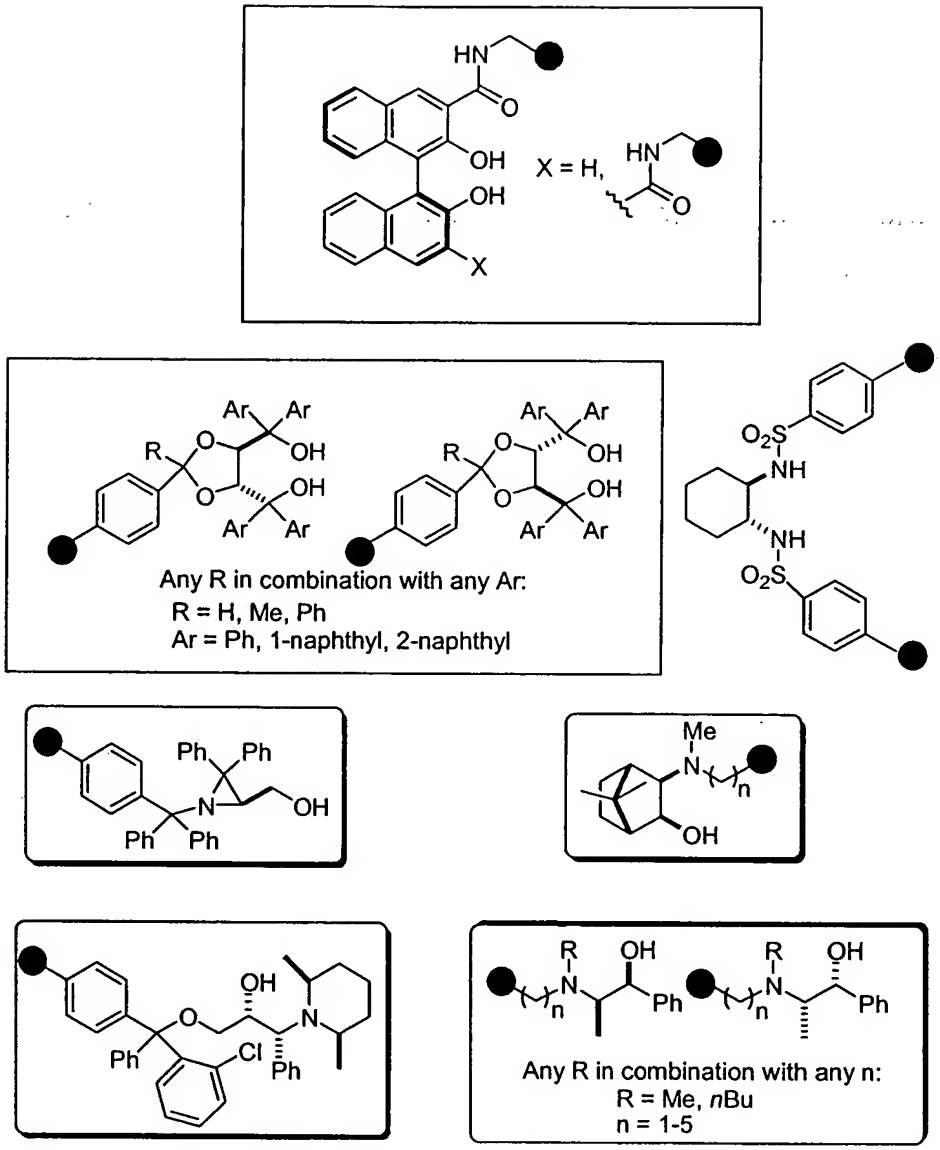
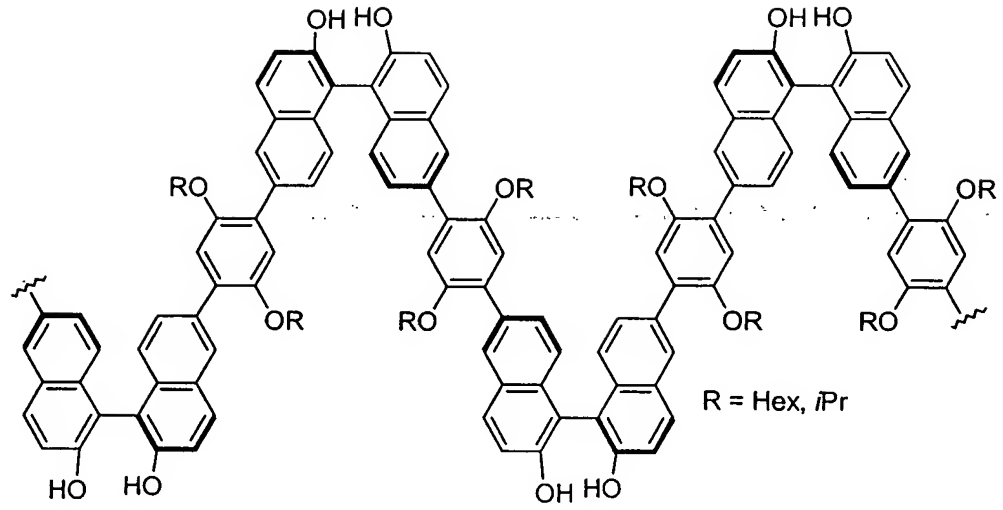

X = H,
Any R in combination with any Ar:
R = H, Me, Ph
Ar = Ph, 1-naphthyl, 2-naphthyl
Any R in combination with any n:
R = Me, nBu
n = 1-5
= an organic polymer or inorganic solid support

Figure 36



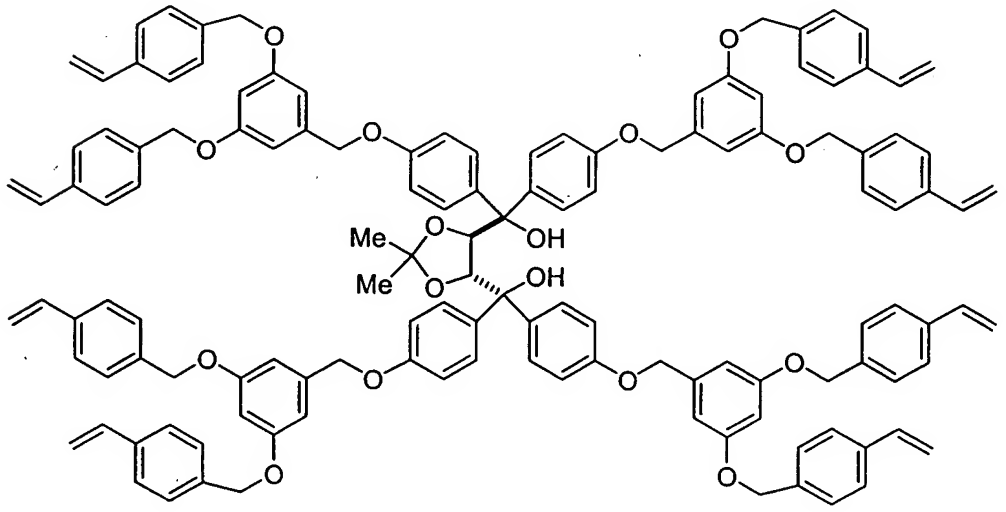


Figure 37

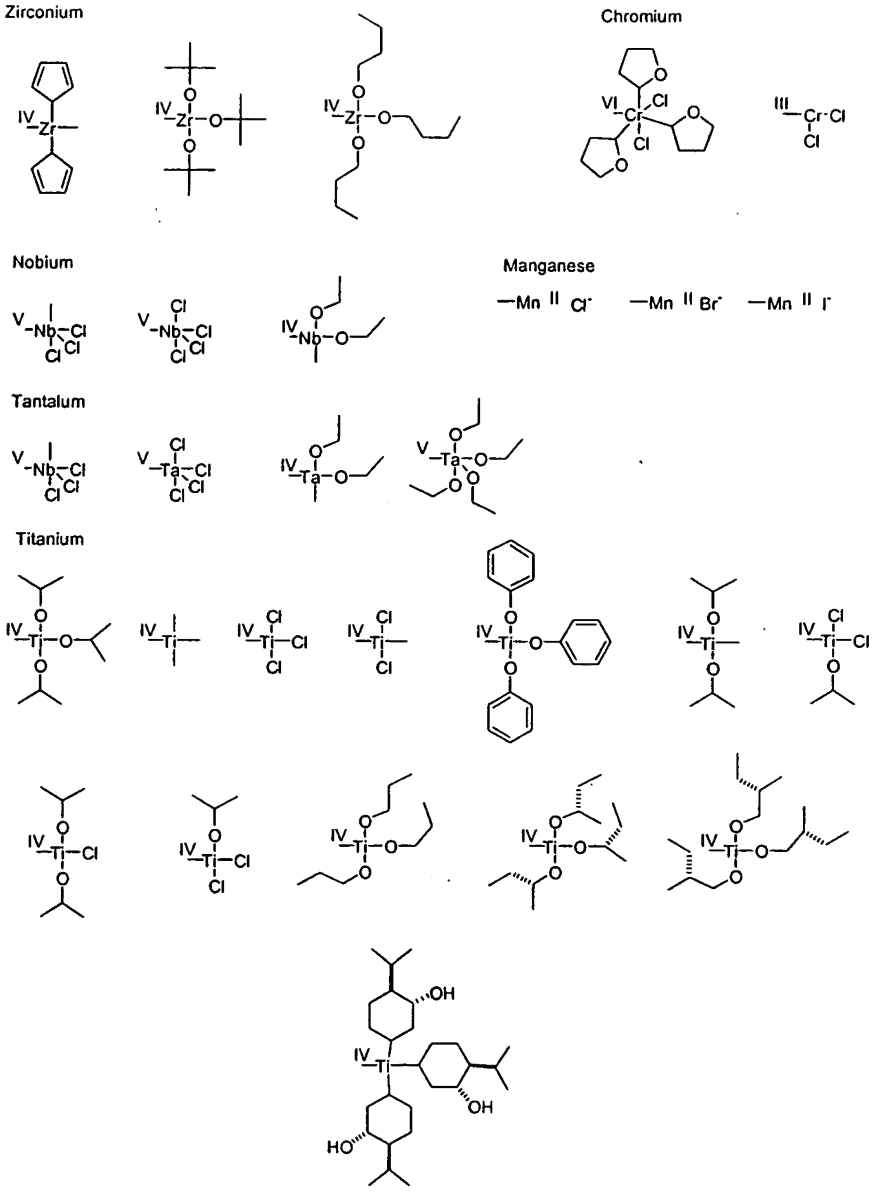

Zirconium
Chromium
Nobium
Manganese
—Mn II Cl
—Mn II Br
—Mn II I
Tantalum
Titanium
OH
OH
HO

Figure 38

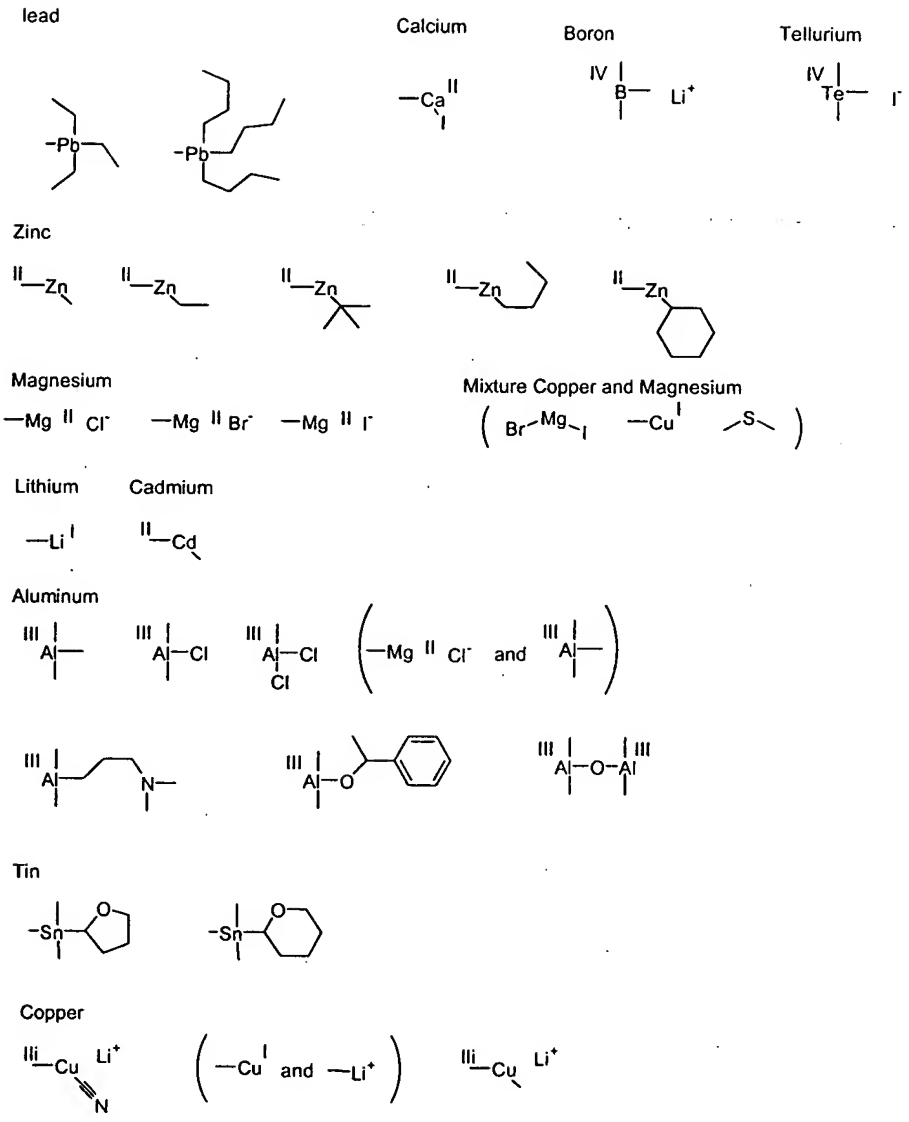

lead
Calcium
Boron
Tellurium
Zinc
Magnesium
Mixture Copper and Magnesium
Lithium
Cadmium
Aluminum
Tin
Copper
and

Figure 39

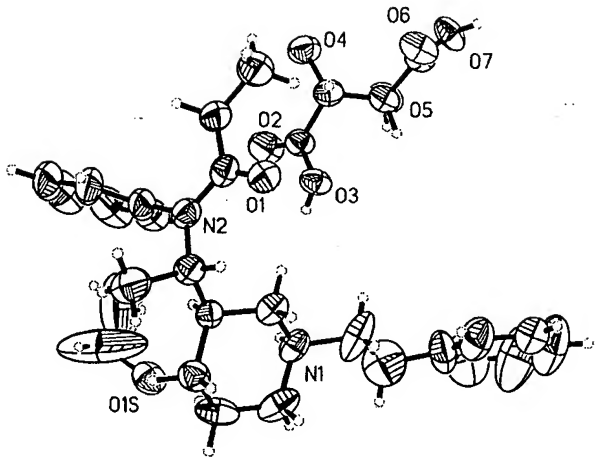


Figure 40

Mixture of 1, 2, 3 and 4:

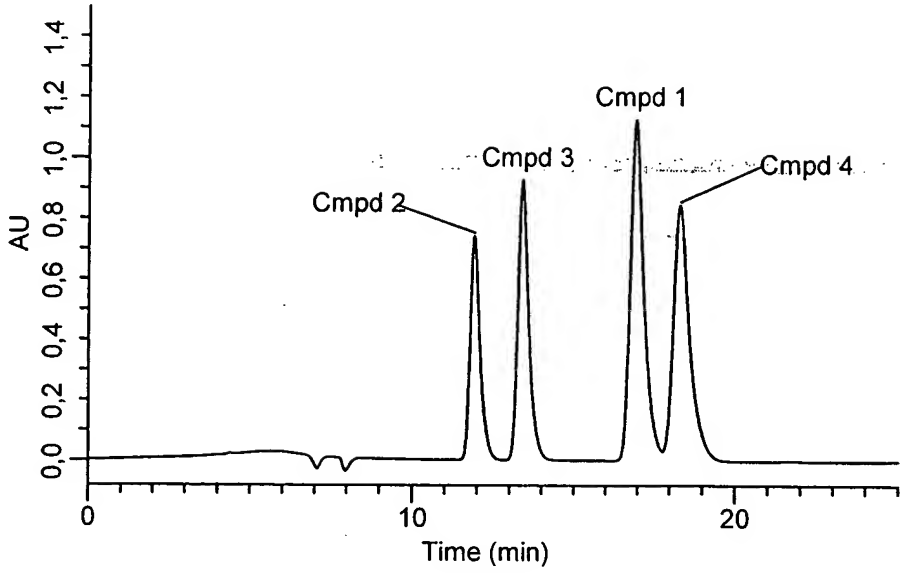


Figure 41

2: (R,S)-Isomer Chromatogram